GDUFA Regulatory Science Update

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Director
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA

GDUFA Regulatory Science Public Meeting
May 20, 2016
GDUFA Regulatory Science Update

• Yearly List of Research Priorities with Stakeholder Input (Public Meetings, Docket)

• FY 2016 Priorities
  - Post-market Evaluation of Generic Drugs
  - Equivalence of Complex Products
  - Equivalence of Locally Acting Products
  - Therapeutic Equivalence Evaluation and Standards
  - Computational and Analytical Tools

• Implementation
  - FDA is engaging with leading pharmaceutical and clinical scientists from across the world to ensure that the regulatory review of generic drugs is based on the best available science.
  - ~100 ongoing external research collaborations (contracts and grants)
    • 10x more resources than pre-GDUFA
  - ORISE research fellows in FDA (OGD and labs)
  - ORS (Office of Research and Standards) staff connects research results to new standards (via guidance, controls, review consults, petition response)
## GDUFA Regulatory Science Scale Up

### OGD Funded GDUFA Science

<table>
<thead>
<tr>
<th>Year</th>
<th>Contracts/Grants ($$) and ORISE</th>
<th>New Contracts/Grants</th>
<th>Cumulative Funds Under Management</th>
<th>Cumulative External Projects Under Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2016</td>
<td>~$20M</td>
<td>~15</td>
<td>$90M</td>
<td>105</td>
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<tr>
<td>FY2015</td>
<td>$26.8M</td>
<td>25</td>
<td>$72M</td>
<td>95</td>
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<tr>
<td>FY2014</td>
<td>$22.8M</td>
<td>35</td>
<td>$54M</td>
<td>76</td>
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<td>FY2013</td>
<td>$20.9M</td>
<td>29</td>
<td>$31M</td>
<td>41</td>
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<td>FY2012</td>
<td>$3.6M</td>
<td>4</td>
<td></td>
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<tr>
<td>FY2011</td>
<td>$2.2M</td>
<td>3</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>FY2010</td>
<td>$3.1M</td>
<td>5</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

FY 2016 numbers are estimates
GDUFA Regulatory Science Impact

• Generic Access in all Product Categories

• Confidence in Generic Drug Substitution

• Better Tools for Development and Review
# Success of Generics

## Non-Discounted Spending and Dispensing by Product Type

<table>
<thead>
<tr>
<th></th>
<th>Spending US$Bn</th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2011</td>
<td>2012</td>
<td>2013</td>
<td>2014</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Total U.S. Market</strong></td>
<td>328.3</td>
<td>317.8</td>
<td>331.5</td>
<td>378.6</td>
<td>424.8</td>
</tr>
<tr>
<td><strong>Brands</strong></td>
<td>74.5%</td>
<td>71.7%</td>
<td>71.0%</td>
<td>72.1%</td>
<td>73.3%</td>
</tr>
<tr>
<td><strong>Unbranded Generics</strong></td>
<td>13.6%</td>
<td>16.1%</td>
<td>16.9%</td>
<td>16.9%</td>
<td>16.0%</td>
</tr>
<tr>
<td><strong>Branded Generics</strong></td>
<td>11.9%</td>
<td>12.2%</td>
<td>12.1%</td>
<td>11.0%</td>
<td>10.7%</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Dispensed prescriptions Mn</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2011</td>
<td>2012</td>
<td>2013</td>
<td>2014</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Total U.S. Market</strong></td>
<td>4,014</td>
<td>4,155</td>
<td>4,236</td>
<td>4,325</td>
<td>4,368</td>
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<tr>
<td><strong>Brands</strong></td>
<td>20.2%</td>
<td>15.9%</td>
<td>13.6%</td>
<td>12.3%</td>
<td>11.3%</td>
</tr>
<tr>
<td><strong>Unbranded Generics</strong></td>
<td>72.7%</td>
<td>77.7%</td>
<td>80.5%</td>
<td>82.1%</td>
<td>83.4%</td>
</tr>
<tr>
<td><strong>Branded Generics</strong></td>
<td>7.1%</td>
<td>6.4%</td>
<td>5.9%</td>
<td>5.6%</td>
<td>5.3%</td>
</tr>
</tbody>
</table>

IMS, *Medicines Use and Spending in the U.S. April 2016*
BE guidance

- Fraction that are for complex products is growing
- New Draft Guidance
  - Ophthalmic emulsion, Otic suspension, Liposomal Injections (3), Sublingual Film, IUD: Subq nanomaterial injection, locally acting GI tablets and capsules
Generic Access in all Product Categories

• Complex Active Ingredients
  – Immunogenicity of peptide impurities, High resolution analytics, multivariate data

• Topical Dermatological Products
  – 9 grants: new in vivo data, characterization of semi-solid formulations, PBPK modeling

• Inhalation Products
  – 9 grants: dissolution, particle size and PK studies, CFD modeling, non Q1-Q2 products

• Ophthalmic Products
  – 9 grants: in vitro characterization, drug release, and drug delivery modeling

• Nasal Products
  – Use of PK studies alone for BE: in vitro, in vivo and modeling projects

• Liposomes and Nanomaterials
  – 7 grants: in vitro release, product characterization, critical manufacturing variables

• Microspheres (Long acting injectables)
  – 9 grants: material characterization, in vitro release, in vivo animal data and modeling
Confidence in Generic Drug Substitution

• **Brand-to-Generic Switching Studies in Patients**
  • All completing studies confirm the conclusions of the studies submitted in the ANDA
  • Change public debate about generic substitution for AED

• **Post-Market Surveillance**
  • Adverse Event Reports: How to interpret for generic substitution
  • Claims and EHR Data: expected substitution patterns for different therapeutic classes, how to compare outcomes and usage patterns

• **Product Specific Standards**
  • NTI Drugs: Tighter BE standards when needed
  • pAUC Comparisons: PK profile similarity when needed
Better Tools for Development and Review

• Models of Non-systemic Absorption
  • 7 grants: PBPK for non-oral delivery

• Pharmacometrics for Generics
  • 5 grants: NTI drugs, pAUC selection, post-approval risk

• Advancing In Vitro Release
  • ~20 grants for complex or locally acting drugs have outcomes of improved drug release, product performance or dissolution methods that can accelerate generic product development
  • Solid Oral: predictive dissolution and oral absorption Models, excipient impact on absorption, pathway for generic versions of abuse-deterrent formulations

• High resolution analytics and multivariate data comparisons
  • ~20 collaborations with FDA labs
Generic Access in all Product Categories: Complex Active Ingredients

• Peptides, complex mixtures, natural source products
• Approval of ANDA for glatiramer acetate
• New Draft Guidance:
  - Conjugated Estrogens
  - Sevelamer Carbonate
  - Omega-3 products
• Guidance Agenda
  - rDNA origin reference peptides guidance pending
  - rDNA origin RLD controls are meeting GDUFA goals
• Research
  - Immunogenicity of peptide related impurities
  - High resolution analytics and multivariate data comparisons
Analyze the Pieces
Evaluate Equivalence of the Product
Generic Access in all Product Categories

Inhalation Products

• Inhalation Product Research
  – Role of dissolution, particle size and PK studies
  – CFD modeling of deposition
  – Non Q1-Q2 inhalation products

• Leads to Guidance
Product-Specific Recommendations for Inhalation Products

Thirteen, as of the April 2016 posting

- Fluticasone propionate/salmeterol Xinafoate DPI (9/13)
- Albuterol MDI (9/13)
- Budesonide/formoterol fumarate MDI (6/15)
- Levalbuterol tartrate MDI (6/15)
- Formoterol fumarate DPI (9/15)
- Aclidinium bromide MDI (9/15)
- Ciclesonide MDI (1/16)
- Beclomethasone dipropionate MDI (1/16)
- Mometasone furoate/formoterol fumarate MDI (1/16)
- Fluticasone furoate/vilanterol trifenatate DPI (4/16)
- Indecaterol maleate DPI (4/16)
- Mometasone furoate MDI (4/16)
Generic Access in all Product Categories
Ophthalmic Products

• **Ophthalmic Products**
  - Nine coordinated grants on in vitro characterization and delivery modeling
  - Modeling and simulation tool chain: PBPK for ophthalmic delivery
    - SimulationsPlus
    - CFD Research
  - In vitro release methods
    - University of Eastern Finland (suspension)
    - Texas A&M (emulsion)
    - University of Connecticut (ointments)

• **Q3 In vitro approach for Q1 and Q2 formulations**
  - Cyclosporine Emulsion (2013)
  - Difluprednate Emulsion (2016)

• **Other Guidance**
  - 10 ophthalmic suspension guidances
  - Research on study designs for aqueous humor PK
  - Q3 approaches
Generic Access in all Product Categories
Nasal Products

• Nasal Products
  – Use of PK studies alone for BE: in vitro, in vivo and modeling projects

• Innovative Technology
  – MDRS particle sizing
  – Instrument first available in 2012
  – ANDA approval in 2016 supported by this technology
Sample

Slide containing the sample

MDRS

API + excipient particle in the slide

Exclusion of agglomerate/ touching particles (solidity filter)

Only API particle for size measurement

Raman id of API; exclusion of excipient particles having overlapping morphology

Classification of excipients using morphology filters (elongation filter)
Generic Access in all Product Categories
Topical Dermatological Products

• Topical Dermatological Products
  – Six coordinated grants (international: US, Europe, Australia) that include
    • New in vivo data
    • Manufacturing of semi-solid formulations
    • Characterization of semi-solid formulations
    • New PBPK modeling approaches
  – Advanced Q3 Equivalence

Topical Drug Products
Clinical endpoint BE studies helped make generics available for only ~23.9% of RLDs
In vivo vasoconstrictor BE studies helped make generic glucocorticoids available for another ~13.8% of RLDs
Total % of topical products with generics ➔ 37.7%
Q3 Testing: Acyclovir 5% Creams

<table>
<thead>
<tr>
<th>Zovirax (USA)</th>
<th>Zovirax (UK)</th>
<th>Zovirax (Austria)</th>
<th>Aciclovad (Austria)</th>
<th>Aciclovir-1A (Austria)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Water</td>
<td>Purified water</td>
<td>Water</td>
<td>Water</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>Liquid Paraffin</td>
<td>Liquid Paraffin</td>
<td>Liquid Paraffin</td>
<td>Viscous Paraffin</td>
</tr>
<tr>
<td>White petrolatum</td>
<td>White soft paraffin</td>
<td>White Vaseline</td>
<td>White Vaseline</td>
<td>White Vaseline</td>
</tr>
<tr>
<td>Cetostearyl alcohol</td>
<td>Cetostearyl alcohol</td>
<td>Cetostearyl alcohol</td>
<td>Cetyl alcohol</td>
<td>Cetyl alcohol</td>
</tr>
<tr>
<td>SLS</td>
<td>SLS</td>
<td>SLS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>Poloxamer 407</td>
<td>Poloxamer 407</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**In Vitro Permeation Test (IVPT)**

6 Donors each with 6 Replicate Skin Sections

**In Vitro Release Test (IVRT)**

**Thixotropic Rheology**

**Density (g/cc)**
- Zovirax (USA): 1.02
- Zovirax (UK): 1.02
- Zovirax (Austria): 1.02
- Aciclovad (Austria): 1.02
- Aciclovir-1A (Austria): 1.01

**Content Uniformity (%)**
- Zovirax (USA): 97.9 ± 0.7
- Zovirax (UK): 99.6 ± 1.4
- Zovirax (Austria): 100 ± 2.2
- Aciclovad (Austria): 99.7 ± 1.7
- Aciclovir-1A (Austria): 98.3 ± 2.6

**Polymorphic Form**
- Zovirax (USA): 2.3 hydrate
- Zovirax (UK): 2.3 hydrate
- Zovirax (Austria): 2.3 hydrate
- Aciclovad (Austria): 2.3 hydrate
- Aciclovir-1A (Austria): 2.3 hydrate

**Crystalline Habit**
- Zovirax (USA): Rectangular
- Zovirax (UK): Rectangular
- Zovirax (Austria): Rectangular
- Aciclovad (Austria): Ovoid
- Aciclovir-1A (Austria): Ovoid

**Particle size (d50) (μm)**
- Zovirax (USA): 3.8
- Zovirax (UK): 2.5
- Zovirax (Austria): 3.4
- Aciclovad (Austria): 6.8
- Aciclovir-1A (Austria): 6

**pH**
- Zovirax (USA): 7.74
- Zovirax (UK): 7.96
- Zovirax (Austria): 7.54
- Aciclovad (Austria): 4.58
- Aciclovir-1A (Austria): 6.05

**Work of Adhesion**
- Zovirax (USA): 59
- Zovirax (UK): 81
- Zovirax (Austria): 60
- Aciclovad (Austria): 17
- Aciclovir-1A (Austria): 18

**Drug in Aq (mg/g)**
- Zovirax (USA): 0.49
- Zovirax (UK): 0.64
- Zovirax (Austria): 0.49
- Aciclovad (Austria): 0.37
- Aciclovir-1A (Austria): 0.26

**Drying Rate (T-30%)**
- Zovirax (USA): >12h
- Zovirax (UK): ~8h
- Zovirax (Austria): ~7h
- Aciclovad (Austria): <1h
- Aciclovir-1A (Austria): <1h

**Water Activity**
- Zovirax (USA): 0.75
- Zovirax (UK): 0.73
- Zovirax (Austria): 0.74
- Aciclovad (Austria): 0.95
- Aciclovir-1A (Austria): 0.95
In Vivo dOFM: (dermal Open Flow Microperfusion)

Dermal Pharmacokinetics by dOFM (20 subjects)

**Outcome variable** | **Cl\(_{90\%}\)**
--- | ---
log(AUC0-36h) | [-0.148 ; 0.162]
| or
| [86.2 % ; 117.5 %]

log(C\(_{\text{max}}\)) | [-0.155 ; 0.190]
| or
| [85.7 % ; 120.9 %]

**Outcome variable** | **Cl\(_{90\%}\)**
--- | ---
log(AUC0-36h) | [-0.369 ; 0.050]
| or
| [69.1 % ; 105.2 %]

log(C\(_{\text{max}}\)) | [-0.498 ; 0.022]
| or
| [60.8 % ; 102.2 %]
Scaled Average BE: Acyclovir Cream 5% IVPT

- Negative Controls for BE: Aciclovir-1A® vs. Zovirax® US

### Aciclovir-1A® (T) vs. Zovirax® US (R)

<table>
<thead>
<tr>
<th>IVPT PK Endpoint</th>
<th>Maximum Flux (Jmax)</th>
<th>Total Bioavailability (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Point Estimate</strong></td>
<td>0.2902</td>
<td>0.3661</td>
</tr>
<tr>
<td><strong>Σ Within Reference</strong></td>
<td>0.5747</td>
<td>0.4193</td>
</tr>
<tr>
<td>SABE [0.80, 1.25]</td>
<td>2.3828 (Non-BE)</td>
<td>1.8843 (Non-BE)</td>
</tr>
<tr>
<td>SABE [0.75, 1.33]</td>
<td>2.2138 (Non-BE)</td>
<td>1.7932 (Non-BE)</td>
</tr>
<tr>
<td>N for [0.80, 1.25]</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>N for [0.75, 1.33]</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

### Aciclovir-1A® (T) vs. Zovirax® US (R)

<table>
<thead>
<tr>
<th>IVPT PK Endpoint</th>
<th>Maximum Flux (Jmax)</th>
<th>Total Bioavailability (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Point Estimate</strong></td>
<td>0.1722</td>
<td>0.1042</td>
</tr>
<tr>
<td><strong>Σ Within Reference</strong></td>
<td>0.5214</td>
<td>0.5512</td>
</tr>
<tr>
<td>SABE [0.80, 1.25]</td>
<td>4.4326 (Non-BE)</td>
<td>7.2356 (Non-BE)</td>
</tr>
<tr>
<td>SABE [0.75, 1.33]</td>
<td>4.2964 (Non-BE)</td>
<td>7.0832 (Non-BE)</td>
</tr>
<tr>
<td>N for [0.80, 1.25]</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>N for [0.75, 1.33]</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
Generic Access in all Product Categories
Liposomes and Nanomaterials

• 7 grants on in vitro release, product characterization and linkage to critical manufacturing variables

• Guidance on Liposomal Injections (3), Subq nanomaterial injection, Ferumoxytol, Sodium ferric gluconate
Generic Access in all Product Categories
Microspheres and LAI

- 9 grants related to material characterization, in vitro release, in vivo animal data and modeling
- Guidance for Risperidone and Naltrexone IM injection
Generic Access in all Product Categories
Complex Drug-Device Combinations

• DPI, MDI, nasal spray, transdermal system, auto-injectors

• New Draft Guidance
  – multiple MDI, DPI, Nasal Spray guidance now available
  • Adhesion for transdermal systems

• Research
  – Irritation for transdermal systems
  – Patient use factors
Generic Access in all Product Categories

Abuse Deterrent Formulations

• Provides a path for generic versions of abuse deterrent opioid formulations
• Relies on comparative in vitro and PK studies

• Essential GDUFA Research
• $500,000 ADF contract with NIPTE (UMD, Purdue) issued in 2013
• ORISE Fellows and equipment in FDA’s DPA and DPQR labs for testing ADF starting in 2013
Confidence in Generic Drug Substitution
Brand-to-Generic Switching Studies in Patients

• All completing studies confirm the conclusions of the studies submitted in the ANDA

• Results on AED and immunosuppressants presented at medical professional societies that have been skeptical of generic substitution
  - American Epilepsy Society Annual meeting
  - American Academy of Neurology Annual meeting
  - Antiepileptic Drug and Device Trials XIII Annual meeting
  - American Transplant Congress meeting
### Study Design

**Outpatients**

- Randomization
- 8 wk
- 2 wk
- Baseline compliance

**Drug over-encapsulated**

### Primary Outcome

**Bioequivalence in Patients**

### Patient Demographics

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male N=20</th>
<th>Female N=15</th>
<th>N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Range (Mean years)</td>
<td>19-66 (44)</td>
<td>20-63 (39)</td>
<td>19-66 (42)</td>
</tr>
<tr>
<td>Epilepsy Focal Generalized</td>
<td>17 3</td>
<td>10 5</td>
<td>27 8</td>
</tr>
<tr>
<td>AED concomitant Valproic acid (inhibitor) Inducer</td>
<td>3 3</td>
<td>0 3</td>
<td>3 6</td>
</tr>
<tr>
<td>Smoking (inducer)</td>
<td>1 2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions None One or more</td>
<td>9 11</td>
<td>4 11</td>
<td>13 22</td>
</tr>
</tbody>
</table>

**Generic to Brand GMR(CI)**

- AUC: 99.4% (97.23-101.61%)
- Cmax: 101.6% (98.79-104.51%)

**Secondary Outcome**

Secondary analysis of seizure control and dose-related adverse events support BE
Generic vs Generic: Multiple Dose Study Design

Study Design

- Randomization
- 2 wk
- 12 hr PK: 19 levels
- MEMS Baseline compliance
- Low Generic
- 2 wk
- High Generic
- Low Generic
- 2 wk
- High Generic
- 12 hr PK
- 2 wk

Patients blinded with product selection

Two levels to assure steady state

Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Sequence 1 (n=14)</th>
<th>Sequence 2 (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42.7 (31.2-55.9)</td>
<td>49.4 (32.6-52.6)</td>
</tr>
<tr>
<td>Previous history of sensitivity to drug product switches</td>
<td>1 (7%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Seizure exacerbations</td>
<td>1 (7%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Increased adverse events</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

Primary Outcome

- Bioequivalence in Patients

Secondary Outcome

- No loss of seizure control
- No unexpected adverse effects and standardized side effect measure scores were not different between generics
“Clearly, this well designed study represents a major step forward in addressing the epilepsy community’s concerns and provides valuable insight regarding AED PK variability.”

“While encouraging, these observations do require confirmation in other patient populations. This issue of individual outliers certainly merits further study.”

“Final data analysis from the EQUIGEN study group (EQUivalence among GENeric AEDs) is near completion and should help further clarify this issue.”
Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial


Summary
Background Patients and clinicians share concerns that generic drug substitution might lead to loss of efficacy or emergence of adverse events. In this trial, we assessed US Food and Drug Administration (FDA) bioequivalence standards by studying the effects of switching between two disparate generic immediate-release lamotrigine products in patients with epilepsy.

The safety of generic substitution in epilepsy
Emilio Perucca
Lancet Neurology, Feb 2016

“The EQUIGEN trial by Michael Privitera and colleagues published in The Lancet Neurology provides strong evidence that, at least for lamotrigine, concerns about generic substitution are largely misplaced.”

“Overall, Privitera and colleagues’ findings are quite reassuring, and organisations with a negative attitude to generic antiepileptic drug substitution should consider reviewing their position.”
Substantial Increase about Patient Preference about Generic Drugs

Variations in Patients’ Perceptions and Use of Generic Drugs: Results of a National Survey

Aaron S. Kesselheim, M.D., J.D., M.P.H.,1,3 Joshua J. Gagne, Pharm.D., Sc.D.,1,3, Jessica M. Franklin, Ph.D.,1,3 Wesley Eddings, Ph.D.,1,3 Lisa A. Fulchino, B.A.,1,3 Jerry Avorn, M.D.,1,3, and Eric G. Campbell, Ph.D.1,3

J Gen Intern Med
DOI: 10.1007/s11606-016-3612-7
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Do you think generic drugs

% (95 % Confidence Interval) respondents answering definitely/probably yes

Are as effective as their brand-name versions

Are as safe as their brand-name versions

Have the same side effects as their brand-name versions

Are made of the same active ingredients as their brand-name versions

How comfortable do you feel:

Asking your doctor to write a prescription for a generic drug if one is available

Taking a generic drug that was prescribed for you by your doctor

If your pharmacist filled the prescription with an FDA-approved generic version of that drug when your doctor prescribed a brand-name drug

If your health insurance company required use of an available and FDA-approved generic version of a brand-name drug that your doctor prescribed*

2014 Survey (Kesseheim et al.)
Over 80%

Patients preferred generics over the brand

2007 Survey (Shrank et al.)
Less than 40%

Non-Caucasians
- prefer brand over generic
- More skeptical of generic drug clinical equivalence
Greater Physician Confidence about Generic Drug Safety and Efficacy

Prevalence and predictors of generic drug skepticism among physicians: Results of a National Survey

*Kesselheim et al.*
*JAMA Internal Medicine, In press*

<table>
<thead>
<tr>
<th>Perceptions</th>
<th>Respondents who strongly or somewhat agree, proportion (%(95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generics are as effective as their corresponding brand-name versions</td>
<td>89 (86-91)</td>
</tr>
<tr>
<td>Generics are as safe as their corresponding brand-name versions</td>
<td>91 (89-93)</td>
</tr>
<tr>
<td>Do not cause more adverse effects than their corresponding brand-name versions</td>
<td>73 (70-76)</td>
</tr>
</tbody>
</table>

2009 Survey (Shrank et al.)
Over 23% expressed negative perceptions

2014 Survey (Kesselheim et al.)
89% believes generic are as effective as the RLD

Further work
- Limiting interactions with pharmaceutical marketing
- Directed educational outreach
Confidence in Generic Drug Substitution
Post-Market Surveillance

Adverse Event Reports
• Which ANDA?
• Potential reporting biases
• How to normalize?
• Research on authorized generics

Claims and EHR Data
• Link to NDC code
• See substitution events
• Research on expected substitution patterns for different therapeutic classes
• Researching how to compare outcomes and usage patterns
Confidence in Generic Drug Substitution
Product Specific Standards

NTI Drugs

- Same BE standards for high and low risk drugs does not build confidence
- Tighter BE standards when needed

pAUC Comparisons

- PK profile differences do not build confidence
- PK profile similarity when needed
- Identify clinically meaningful time points
Better Tools for Development and Review
Pharmacometrics for Generics

NTI Drugs
• Exposure response analysis for identifying NTI drugs
• Draft Guidance:
  – tacrolimus ER, phenytoin, levothyroxine, carbamazepine
• Petition Response
  – Not needed for dalfampridine

pAUC Comparisons
• PK/PD models to identify when pAUC for BE are needed
• Draft Guidance:
  – methylphenidate products
• Petition Response
  – No pAUC for Naproxen/Esomeprazole
Better Tools for Development and Review
Non-systemic Absorption

Drug substance Formulations
In vitro performance

Model

In vivo performance

7 grants on PBPK for non-oral delivery routes
Better Tools for Development and Review
Advancing In Vitro Release

• Solid Oral Dosage forms
  – Predictive Dissolution and Oral Absorption Models
  – Excipient impact on absorption
  – Pathway for generic versions of abuse-deterrent formulations

• Complex or Locally Acting Drugs
  – ~20 grants have outcomes of improved drug release, product performance or dissolution methods that can accelerate generic product development for complex or locally acting drugs
GDUFA Regulatory Science
Input Requested Today

• Generic Access in all Product Categories

• Confidence in Generic Drug Substitution

• Better Tools for Development and Review
Summary

• Huge public health impact for small regulatory science investments

• Access
  - Access to $billion markets
  - Guidance on complex products
  - FDA research aids internal alignment on complex issues

• Confidence
  - FDA science supports public perceptions

• Faster Development and Review
  - Analytical tools
  - Modeling & simulation tools